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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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CHRISTENSEN, O'CONNOR, JOHNSON, KINDNESS, PLLC
1420 FIFTH AVENUE
SUITE 2800
SEATTLE, WA 98101-2347

EXAMINER	
GIBBS, TERRA C	
ART UNIT	**PAPER NUMBER**
1635	13

DATE MAILED: 10/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,770	BORNSTEIN ET AL.	
	Examin r	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10-18 and 28-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10-18 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Amendment filed July 28, 2003, in Paper No. 12.

New claims 28-32 are acknowledged. Claims 1-7, 10-18, and 28-32 are pending in the instant application.

Claims 8, 9, and 19-27 have been canceled. Thrombospondin 2 antagonists: anti-thrombospondin 2 antibody and a thrombospondin 2 blocking peptide are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely made the election without traverse on November 14, 2002.

Specification

The objection to the Specification is withdrawn in view of Applicants Amendment to correct for embedded hyperlinks and/or other forms of browser-executable codes filed in Paper No. 12.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7 and 10-18 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. This rejection is maintained (in part) in view of Applicants arguments, filed July 28, 2003.

Applicants argue that the subject matter is clearly defined by its percentage of sequence identity to the complement of the TSP2 cDNA set forth in SEQ ID NO:3. Applicants further argue that a method for determining the percentage of sequence identity is set forth in the instant Specification at page 7, lines 1-9. Applicants also argue that the antisense thrombospondin nucleic acid molecules are described as "hybridizing under stringent conditions" and the term, "hybridizing under stringent conditions" is described in the instant Specification at page 6, lines 4-19.

Applicant's arguments have been fully considered, but are found persuasive (in part). First, Applicants argue that the subject matter is clearly defined by its percentage of sequence identity to the complement of the TSP2 cDNA set forth in SEQ ID NO:3. This is not found persuasive because claim 1 encompasses molecules that specifically hybridize all forms of the thrombospondin 2 or the osteopontin gene, which includes sequences from other species, mutated sequences, polymorphic and allelic variants, splice variants, sequences that have an unspecified degree of identity (similarity, homology), and so forth. The instant specification as filed provides only a description of the thrombospondin 2 gene (see SEQ ID NO:3) and the osteopontin gene (SEQ ID NO:1). However, the specification as filed, does not provide a sufficient description that would allow one of skill in the art to use SEQ ID NO:3 or SEQ ID NO:1 to predict the structures of *any/all* molecules that modulate thrombospondin 2 or osteopontin, including those isolated from other sources, including all polymorphic, allelic and splice variants of these genes. Additionally, claim 1 is so broad to include any thrombospondin 2

antagonist. The specification as filed, does not provide a sufficient description that would allow one of skill in the art to use SEQ ID NO. 3 to predict the structure of a small organic molecule that is a thrombospondin 2 antagonist, for example. Therefore, Applicant's specification does not provide a sufficient number of representative species of molecules that modulate thrombospondin 2 or osteopontin which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds.

Second, the Examiner aggress the antisense thrombospondin nucleic acid molecules are clearly described as "hybridizing under stringent conditions". Therefore, the 35 U.S.C. 112 rejection for written description is maintained on the grounds that claim 1 is so broad to include molecules that specifically hybridize all forms of the thrombospondin 2 or the osteopontin gene, which includes sequences from other species, mutated sequences, polymorphic and allelic variants, splice variants, sequences that have an unspecified degree of identity (similarity, homology), and so forth, where the instant Specification has only described SEQ ID NOs:1 and 3, corresponding to the osteopontin gene and the thrombospondin 2 gene, respectively.

Claims 1-7 and 10-18 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained (in part) in view of Applicants arguments, filed July 28, 2003.

Applicants argue that the instant Specification discloses at least one method for effectively delivering antisense thrombospondin 2 nucleic acid molecules to a mammalian

subject, by incorporating the antisense nucleic acid molecules into the surface layer of an implanted medical device, and said incorporation improves vascularization of the foreign body that forms around the implanted device. Applicants also argue that the mouse is an art-recognized model for studying the mammalian would response. Applicants rely on Attachments A-F to demonstrate that mouse is a useful model system for studying blood vessel formation, and that results observed in mice can be extrapolated to humans. Applicants further argue that while the art met some difficulties in assessing the efficacy of antisense treatments to decrease thrombospondin expression, biological changes were observed nonetheless. Applicants also argue that it is well within the ability of one of ordinary skill in the art to make and use effective antisense *in vivo*.

Applicant's arguments have been fully considered but are found persuasive (in part). In view of Applicants arguments, the 35 U.S.C. 112, first paragraph for full enablement is maintained in light of the new scope of enablement rejection as follows:

Claims 1-7 and 10-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing blood vessel density in an animal comprising the local administration of a thrombospondin 2 antisense nucleic acid (SEQ ID NO:3) impregnated in an implant device, does not reasonably provide enablement for a method of modulating the biological activity of thrombospondin 2 or osteopontin in an animal comprising the introduction of a thrombospondin 2 antagonist or an osteopontin molecule that modulates thrombospondin 2 or osteopontin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-7 and 10-18 are drawn to a method of modulating the biological activity of thrombospondin 2 or osteopontin in an animal comprising the introduction of a thrombospondin 2 antagonist or an osteopontin molecule that modulates thrombospondin 2 or osteopontin.

The instant invention specification provides methodologies for locally delivering antisense thrombospondin 2 nucleic acid molecules to a mammalian subject, by incorporating the antisense nucleic acid molecules into the surface layer of an implanted medical device and improving vascularization of the foreign body that forms around the implanted device (see Examples 1 and 2).

Verma et al. (Nature, 1997 Vol. 389:239-242) teach the problems of gene delivery in whole organisms suffers from limitations relating to poor efficiency of delivery and the transient expression of delivered genes (page 239, second paragraph from the end).

As argued in the previous Office Action, filed January 31, 2003, there is considerable unpredictability in using antisense nucleic acid *in vivo*. Applicants, in response to this statement argue that it is well within the ability of one of ordinary skill in the art to make and use effective antisense *in vivo*. In view of Applicants arguments and the unpredictability in the art, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention over the scope claimed without having to engage in trial and error or undue experimentation. The specification as filed contemplates a method of modulating the biological activity of thrombospondin 2 or osteopontin in an animal comprising the introduction of a thrombospondin 2 antagonist or an osteopontin molecule that modulates thrombospondin 2 or osteopontin. However, it is unclear how a method of increasing blood vessel density in an animal comprising the local

administration of a thrombospondin 2 antisense nucleic acid (SEQ ID NO:3) impregnated in an implant device is correlated with/or representative of a method of modulating the biological activity of osteopontin in an animal comprising the introduction of a thrombospondin 2 antisense nucleic acid molecule that modulates osteopontin, for example. It is also unclear how any thrombospondin 2 antisense will modulate (e.g. increase) thrombospondin 2 biological activity *in vivo* where no specific guidance (i.e. specific mode of treatment, delivery route, tissue specificity, etc.) is provided.

The specification does not provide particular guidance or particular direction a method of modulating the biological activity of osteopontin in an animal comprising the introduction of a thrombospondin 2 antisense nucleic acid molecule that modulates osteopontin in an animal. The specification does not provide guidance for the delivery of antisense thrombospondin 2 into the target organ and target cells in an animal in quantity sufficient to modulate osteopontin biological activity. While the specification provides guidance to locally delivering antisense thrombospondin 2 nucleic acid molecules to a mammalian subject, by incorporating the antisense nucleic acid molecules into the surface layer of an implanted medical device and improving vascularization of the foreign body that forms around the implanted device, the specification provides no particular nexus between modulating osteopontin biological activity or modulating (e.g. increase) thrombospondin 2 biological activity using a thrombospondin antisense, as contemplated by the specification. The specification provides no particular guidance of direction for addressing the problems of targeting, permanence and quantity of modulation of the osteopontin gene in question, immunogenicity, etc, for antisense targeting thrombospondin 2, in an animal.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate with the full scope of the claims. Due to the lack of specific guidance in the specification as filed and the lack of correlation between a method of increasing blood vessel density in an animal comprising the local administration of a thrombospondin 2 antisense nucleic acid (SEQ ID NO:3) impregnated in an implant device, and a method of modulating the biological activity of osteopontin in an animal comprising the introduction of a thrombospondin 2 antagonist that modulates osteopontin, one of skill in the art would require specific guidance to practice the current invention. The current specification does not provide such guidance to modulating osteopontin biological activity using a thrombospondin 2 antisense nucleic acid *in vivo* and one of skill in the art would be required to perform trial and error or undue experimentation. The quantity of experimentation required to practice the invention over the scope claimed would include the sufficient systemic delivery of a thrombospondin 2 antisense nucleic acid to specific intracellular targets in quantities sufficient to modulate thrombospondin 2 biological activity in an animal; and sufficient delivery of a thrombospondin 2 antisense nucleic acid to specific intracellular targets in quantities sufficient to modulate osteopontin biological activity in an animal. Therefore, undue experimentation would be required of a person of skill in the art to make and use the claimed invention, particularly, in view of the obstacles needed to overcome to use antisense therapy methods as exemplified in the references discussed in the previous Office Action and Verma et al. above. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the

broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Accordingly, limiting the scope of the claimed invention to a method of increasing blood vessel density in an animal comprising the local administration of a thrombospondin 2 antisense nucleic acid (SEQ ID NO:3) impregnated in an implant device is proper.

Claims 1-7 and 10-18 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained (in part) in view of Applicants arguments, filed July 28, 2003.

Applicants argue that the instant Specification discloses at least one method for effectively delivering osteopontin molecules to a mammalian subject, by incorporating the osteopontin molecules into the surface layer of an implanted medical device, said incorporation reduces fibrous capsule thickness and macrophage infiltration surrounding the implanted devise. Applicants also argue that the mouse is an art-recognized model for studying the mammalian would response. Applicants rely on Attachments A-F to demonstrate that mouse is a useful model system for studying blood vessel formation, and that results observed in mice can be extrapolated to humans. Applicants further argue that while the art asserts that the precise role of osteopontin *in vivo* remains unclear, they are not required to fully understand all the functions of osteopontin in a living subject. Applicants also argue that the instant Specification is fully

enabled and the instant application provides sufficient information to teach one of skill in the art how to use osteopontin to modulate the wound response in an animal.

Applicant's arguments have been fully considered but are found persuasive (in part). In view of Applicants arguments, the 35 U.S.C. 112, first paragraph for full enablement is maintained in light of the new scope of enablement rejection as follows:

Claims 1-7 and 10-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing fibrous capsule thickness and macrophage infiltration in an animal comprising the local administration of osteopontin immobilized in an implant device, does not reasonably provide enablement for a method of modulating the biological activity of thrombospondin 2 or osteopontin in an animal comprising the introduction of a thrombospondin 2 antagonist or an osteopontin molecule that modulates thrombospondin 2 or osteopontin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-7 and 10-18 are drawn to a method of modulating the biological activity of thrombospondin 2 or osteopontin in an animal comprising the introduction of a thrombospondin 2 antagonist or an osteopontin molecule that modulates thrombospondin 2 or osteopontin.

The instant invention specification provides methodologies for reducing fibrous capsule thickness and macrophage infiltration in an animal comprising the local administration of osteopontin immobilized in an implant device (see Example 3).

As argued in the previous Office Action, filed January 31, 2003, there is considerable unpredictability in using osteopontin *in vivo* (see O'Reagen et al.). Applicants, in response to

this statement argue that they are not required to fully understand all the functions of osteopontin in a living subject. In view of Applicants arguments and the unpredictability in the art, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention over the scope claimed without having to engage in trial and error or undue experimentation. The specification as filed contemplates a method of modulating the biological activity of thrombospondin 2 or osteopontin in an animal comprising the introduction of a thrombospondin 2 antagonist or an osteopontin molecule that modulates thrombospondin 2 or osteopontin. However, it is unclear how reducing fibrous capsule thickness and macrophage infiltration in an animal comprising the local administration of osteopontin immobilized in an implant device is correlated with/or representative of a method of modulating the biological activity of thrombospondin 2 in an animal comprising the introduction of a osteopontin molecule that modulates thrombospondin 2, for example. It is also unclear how any osteopontin molecule will modulate (e.g. decrease) osteopontin biological activity *in vivo* where no specific guidance (i.e. specific mode of treatment, delivery route, tissue specificity, etc.) is provided.

The specification does not provide particular guidance or particular direction a method of modulating the biological activity of thrombospondin 2 in an animal comprising the introduction of an osteopontin molecule that modulates thrombospondin 2 in an animal. The specification does not provide guidance for the delivery of osteopontin into the target organ and target cells in an animal in quantity sufficient to modulate thrombospondin 2 biological activity. While the specification provides guidance to reducing fibrous capsule thickness and macrophage infiltration in an animal comprising the local administration of osteopontin immobilized in an

implant device, the specification provides no particular nexus between modulating thrombospondin 2 biological activity or modulating (e.g. decrease) osteopontin biological activity using a osteopontin molecule, as contemplated by the specification. The specification provides no particular guidance of direction for addressing the problems of targeting, permanence and quantity of modulation of the thrombospondin gene in question, immunogenicity, etc, for an osteopontin molecule, in an animal.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate with the full scope of the claims. Due to the lack of specific guidance in the specification as filed and the lack of correlation between reducing fibrous capsule thickness and macrophage infiltration in an animal comprising the local administration of osteopontin immobilized in an implant device, and a method of modulating the biological activity of thrombospondin 2 or osteopontin in an animal comprising the introduction of a thrombospondin 2 antagonist or an osteopontin molecule that modulates thrombospondin 2 or osteopontin, one of skill in the art would require specific guidance to practice the current invention. The current specification does not provide such guidance to modulating thrombospondin 2 biological activity using an osteopontin molecule *in vivo* and one of skill in the art would be required to perform trial and error or undue experimentation. The quantity of experimentation required to practice the invention over the scope claimed would include the sufficient systemic delivery of an osteopontin molecule to specific intracellular targets in quantities sufficient to modulate osteopontin biological activity in an animal; and sufficient

delivery of an osteopontin molecule to specific intracellular targets in quantities sufficient to modulate thrombospondin 2 biological activity in an animal. Therefore, undue experimentation would be required of a person of skill in the art to make and use the claimed invention, particularly, in view of the unpredictability of using osteopontin *in vivo*, as exemplified in the references discussed in the previous Office Action (see O'Reagen et al.). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Accordingly, limiting the scope of the claimed invention to a method of reducing fibrous capsule thickness and macrophage infiltration in an animal comprising the local administration of osteopontin immobilized in an implant device is proper.

Claim Rejections - 35 USC § 102

Claims 1 and 11 were rejected under 35 U.S.C. 102(b) as being anticipated by Liaw et al. (Journal of Clinical Investigation, 1998 Vol. 101:1468-1478). This rejection is maintained for the reasons of record set forth in the previous Office Action, filed January 31, 2003.

Applicants argue that Liaw et al. teaches the use of an osteopontin replacement vector in which exons 4-7 of osteopontin are replaced by a marker, thereby inactivating the osteopontin gene.

While the Examiner agrees that Liaw et al disclose the use of an osteopontin replacement vector in which exons 4-7 of osteopontin are replaced by a marker, this replacement vector contains exons 1-3 of osteopontin which includes a portion of the osteopontin coding region (see Liaw et al. Figure 2) and thus represents the introduction of osteopontin. As Applicant has

confirmed, the replacement vector disclosed by Liaw et al. inactivates the osteopontin gene, and thus represents modulation of osteopontin biological activity. Since the claims are so broad to include the modulation (e.g. increase or decrease) of the biological activity of osteopontin comprising the introduction of osteopontin to modulate the biological activity of osteopontin, Liaw et al. anticipate claims 1 and 11.

Claims 1 and 11 were rejected under 35 U.S.C. 102(b) as being anticipated by Gardner et al. (Oncogene, 1994 Vol. 9:2321-2326). This rejection is withdrawn in view of Applicants arguments, filed July 28, 2003.

Claims 1 and 11 were rejected under 35 U.S.C. 102(a) as being anticipated by Okada et al. (American Journal of Physiological and Renal Physiology, 2000 Vol. 278:F110-F121). This rejection is withdrawn in view of Applicants arguments, filed July 28, 2003.

Claims 1-7 and 10 were rejected under 35 U.S.C. 102(e) as being anticipated by Streit et al. [U.S. Publication No: 2002/0119921]. This rejection is withdrawn in view of Applicants arguments, filed July 28, 2003.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 11, 12 and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Peterson et al. [WO 99/33415].

Claims 1 and 11 are drawn to a method of modulating the biological activity of thrombospondin 2 or osteopontin in an animal comprising the introduction of a thrombospondin 2 antagonist or an osteopontin molecule that modulates thrombospondin 2 or osteopontin. Claim 12 and 15 are dependent on claim 1 and include all the limitations of claim 1, with the further limitations wherein the molecule is introduced into the animal by injection, as a component of an implanted porous matrix, or by immobilization onto an implanted surface; and wherein the animal is exhibiting a wound response.

Peterson et al. disclose Sprague Dawley rats with a circular intraosseous wound defect exhibit growth of bone tissue following osteopontin introduction. Peterson et al. further disclose an osteopontin composition comprising an osmotic pump, implanted subcultaneously in Sprague Dawley rats, is connected to a catheter wherein the catheter directs delivery of the pumps contents (osteopontin) into the circular intraosseous wound defect of the rat (see Example 1). Peterson et al. further disclose the introduction of osteopontin into the rat circular intraosseous wound defect via the osmotic pump method enhances new bone formation (see Table 1).

Therefore Peterson et al. anticipate claims 1, 11, 12 and 15.

Claims 1-5, 10, 12, 28 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Detmar et al. [WO 00/57899].

Claim 1 and 2 are drawn to a method of modulating the biological activity of thrombospondin 2 or osteopontin in an animal comprising the introduction of a thrombospondin 2 antagonist or an osteopontin molecule that modulates thrombospondin 2 or osteopontin. Claims 3-5, 10 and 12 are dependent on claim 1 and include all the limitations of claim 1, with

the further limitations wherein the biological activity of thrombospondin 2 is decreased, wherein the antagonist of thrombospondin 2 is an antisense thrombospondin 2 nucleic acid molecule; wherein the antagonist of thrombospondin 2 is a thrombospondin 2 ribozyme; wherein the antisense thrombospondin 2 nucleic acid molecule or thrombospondin 2 ribozyme is introduced in the animal; and wherein the molecule is introduced into the animal by injection. Claim 28 is drawn to a method of modulating the biological activity of thrombospondin 2 or osteopontin in an animal comprising the introduction of a structure comprising an agent wherein the agent is a thrombospondin 2 antagonist or an osteopontin molecule that modulates thrombospondin 2 or osteopontin. Claim 29 is dependent on claim 28 and includes all the limitations of claim 28, with the further limitation wherein the agent is an antisense thrombospondin 2 nucleic acid molecule.

Detmar et al. disclose a method of treating a subject comprising administering an agent which decreases thrombospondin 2 activity (see claims 26, 27 and 36). Detmar et al. further disclose the agent which decreases thrombospondin 2 activity is a thrombospondin 2 nucleic acid molecule that can bind to cellular thrombospondin 2 mRNA and inhibit expression of the protein (e.g. an antisense molecule or ribozyme) (see page 9, lines 16 and 17). Detmar et al. further disclose the thrombospondin 2 nucleic acid molecule as Figure 2. It is noted that the Figure 2 disclosure of Detmar et al. is 100% identical to SEQ ID NO:3 of the instant invention. Detmar et al. further disclose the agent which decreases thrombospondin 2 activity is administered intravenously (see page 10, line 2).

Therefore Detmar et al. anticipate claims 1-5, 10, 12, 28 and 29.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 28-32 are drawn to method of modulating the biological activity of osteopontin in an animal comprising the introduction of a structure comprising an agent of osteopontin that is at least 70% identical to an osteopontin molecule consisting of the amino acid sequence set forth in SEQ ID NO:2, wherein the agent modulates the biological activity of osteopontin.

The claimed invention encompasses an agent of osteopontin that is at least 70% identical to an osteopontin molecule consisting of the amino acid sequence set forth in SEQ ID NO:2. The specification as filed provides only a description of the osteopontin gene (SEQ ID NO:2). The issue is that the instant Specification has not disclosed the structure or physical properties of an agent of osteopontin that are at least 70% identical to an osteopontin molecule consisting of the amino acid sequence set forth in SEQ ID NO:2 that modulates the biological activity of osteopontin as recited in claim 28. The specification as filed, does not provide sufficient description that would allow one of skill in the art to use SEQ ID NO:2 to predict the structures any/all agents of osteopontin that are at least 70% identical to an osteopontin molecule consisting of the amino acid sequence set forth in SEQ ID NO:2 that modulates the biological activity of osteopontin.

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

Additionally, "[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims

directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence."

Applicant's specification does not provide a sufficient number of representative species of an agent of osteopontin that are at least 70% identical to an osteopontin molecule consisting of the amino acid sequence set forth in SEQ ID NO:2 that modulates the biological activity of osteopontin, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Information Disclosure Statement

The Information Disclosure Statement, filed February 11, 2003 in Paper No. 10 is acknowledged. The references referred to therein have been considered on the merits.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
October 14, 2003

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER